DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

I-011468-Z-0026-OO

U.S. Fish & Wildlife Service
Aquatic Animal Drug Approval Partnership (AADAP)
Attention: Dave Erdahl
Program Director, AADAP
4050 Bridger Canyon Rd.
Bozeman, MT 59715

Re: Memorandum of Conference for Meeting on October 12, 2011

Dear Dr. Erdahl:

I am enclosing a copy of the Center for Veterinary Medicine's (CVM) Memorandum of Conference (MOC) summarizing our meeting of October 12, 2011. At this meeting, we discussed the product development plan for the approval of channel catfish pituitary for use as a spawning aid. Specifically, we discussed requirements for target animal safety, effectiveness, chemistry and manufacturing, the environmental assessment, the all other information and labeling technical sections. We answered specific questions posed in your meeting request. CVM's MOC is the official record of this meeting.

If you would like to request specific changes to, or clarification of, our MOC, you must send your request within 30 days of the date of this letter. The request should specifically outline your questions, identify areas you would like clarified, and request any corrections you would like us to make to the MOC. Please do not raise issues unrelated to the meeting in your letter, because they will delay our response to your request for any changes to or clarifications of our MOC. We will send you a response no later than 45 days after the date of receipt of the request.

In addition, we have the following comments:

- CVM indicated that they would provide the sponsor with more specific information regarding the number of animals that may be necessary to demonstrate that the target success rate was achieved in effectiveness studies. The following table showing the number of fish required to meet specified criteria for varying results will help determine the number of fish needed for the study. For example, if the target success rate was 70% and the observed success rate was 80%, an experiment having 62 fish in the treated group will result in the 95% CI limit being above the 70% target. (Note that variance can fluctuate depending on the sample size.)

Target success rate	Observed success rate					
	65%	70%	75%	80%	85%	90%
60%	350	81	33	16	8	4
70%			289	62	22	9
80%					196	35

Concerning your question regarding eligibility for a MUMS grant to support development of a bioassay, we have the following comments. The Minor Use/Minor Species (MUMS) Grant Program was established by the Minor Use and Minor Species Animal Health Act of 2004. In accordance with the statute, a MUMS grant must be for the purpose of defraying the costs of qualified safety and effectiveness testing expenses incurred in connection with the development of designated new animal drugs. If your proposed bioassay supports only the CMC technical section, development of the assay would not be eligible for grant funding through this program. If you have any questions concerning the MUMS Grant Program, please contact Dr. Stuart Jeffrey at (240) 276-8604 or Dr. Joan Gotthardt at (240) 276-9331.

If you submit correspondence relating to this letter, you should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments please contact me at (240) 276-8349. You may also contact Jennifer Love, Project Manager at (240) 276-8358.

Sincerely,

{see appended electronic signature page}
Aila Albrecht, PMP
Project Manager
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

Enclosure<s>:
Memorandum of Conference held October 12, 2011

Electronic Signature
Addendum for Submission ID

I-011468-Z-0026-OO

Signing Authority (Role)	Letter Date
Aila Albrecht (Team Leader)	11/23/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

I-011468-Q-0026-OO
(channel catfish pituitary)
Channel Catfish
U.S. Fish & Wildlife Service
Aquatic Animal Drug Approval Partnership

MEMORANDUM OF CONFERENCE
October 12, 2011

Background

U.S. Fish & Wildlife Service Aquatic Animal Drug Approval Partnership requested a meeting with CVM to discuss the product development plan for the approval of channel catfish pituitary for use as a spawning aid. In their request, they included specific questions regarding efficacy, target animal safety, chemistry and manufacturing and completion of the environmental assessment. An amendment to this request (I-011468 T-0027) was received on August 16, 2011.

There is currently a submission under review (I-011468-P-0023-NV). An ERA has been requested for this submission.

The following U.S. Fish and Wildlife Service and CVM personnel attended the meeting:

U.S. Fish and Wildlife	CVM
Jim Bowker	Jennifer Love, Project Management Team
Chris Green	James Nitao, Biotherapeutics Team, Division of Manufacturing Technologies
Pat Gaunt	Michael Popek, Biotherapeutics Team, Division of Manufacturing Technologies
Tom Bell	Charles Eirkson, Environmental Safety Team, Division of Scientific Support
Roger Yant	Cindy Burnsteel, Division of Therapeutic Drugs for Food Animals
	Eric Landis, Aquaculture Drugs Team, Division of Therapeutic Drugs for Food Animals
	Jennifer Matysczak, Aquaculture Drugs Team, Division of Therapeutic Drugs for Food Animals
	Veronica Taylor, Biostatistics Team 2, Division of Scientific Support
	Wei Zhang, Biostatistics Team 2, Division of Scientific Support
	Eric Silberhorn, Environmental Safety Team, Division of Scientific Support
	Holly Zahner, Environmental Safety Team, Division of Scientific Support
	Stacey Gore, Aquaculture Drugs Team, Division of Therapeutic Drugs for Food Animals
	Aila Albrecht, Project Management Team

Discussion

Environmental Safety Comments

CVM informed the sponsor that a cursory review of the environmental assessment (EA) prepared by AADAP that is currently in-house has been completed. The EA will require revisions in order to support preparation of a Finding of No Significant Impact (FONSI) and a technical section complete letter. At this time, the EA has not adequately addressed the potential indirect effects of the hybridization of channel x blue catfish. Specifically, the EA needs to address the likelihood that the hybrid catfish will escape from production facilities and the potential consequences if hybrids do, in fact, escape confinement. This would include addressing the potential for escapees to survive, reproduce and establish a population(s) in the natural environment. Ultimately, the EA needs to evaluate and determine if risks to the environment are significant or not.

Based on the information in the EA and additional research conducted by CVM, CVM agreed that there is currently no federal oversight to regulate the production and containment of hybrid fish in the United States. The responsibility for containment and regulation of hybrid species, if needed, likely resides with the individual States. CVM agreed with the sponsor's recommendation to provide examples of States that have regulatory programs or systems for permitting and/or containment of non-indigenous species in the EA. CVM advised the sponsor that either a minor amendment and/or an end review amendment (ERA) will be needed to address both the structural (formatting) and content issues within the EA. A reorganization of the document and additional text will be needed to delineate discussions of direct (drug-related) and indirect (fish-related) effects; CVM will provide specific direction in this regard in the near future. Further, CVM advised that if the proposed indication includes "a variety of warmwater finfish species", then the scope of the EA will need to be significantly expanded to include information on potential environmental effects due to use in a wider variety of finfish species. If the proposed claim includes fish species other than catfish of the genus *Ictalurus*, we recommend that the Environmental Safety Team be contacted to discuss changes to the scope of the EA.

Chemistry, Manufacturing, and Controls (CMC) Comments

The sponsor stated the product will consist of crude catfish pituitary gland. The sponsor stated that the hypothalamus produces luteinizing hormone-releasing hormone (LHRH), which stimulates the pituitary to produce and release luteinizing hormone (LH). The primary active component in the product is believed to be LH.

Prior to the meeting, the sponsor submitted the following agenda item for discussion by CVM:

1. We propose an assay such as that described below to verify product purity

> *a. An ELISA assay for luteinizing hormone will be administered to quantify the active gonadotropin responsible for final oocyte maturation in CP.*
>
> *b. The LH ELISA will be validated by administration of Gonadotropin releasing hormone.*
>
> > *i. Gravid female channel catfish (n = 7 per triplicate) will be injected with standard priming and resolving doses at 20 and 80 μg/kg, respectively, of LHRHa.*

ii. Blood plasma will be processed and assayed for channel catfish LH through standard procedures using the developed ELISA.

c. To further characterize the specific biochemical response to hormone application the concentrations of plasma estradiol and testosterone will be determined. Oocytes from a sub sample of females will be sampled throughout this period to record yolk coalescence, clearing, and germinal vesicle migration.

Subsequent to the submission of the agenda, and several days before the meeting, the sponsor submitted a new document titled "Develop in vitro bioassays for assessing biological potency of CP using tissues from channel catfish". The document states the sponsor will explore alternative approaches to an ELISA method. During the meeting, the sponsor explained that it had submitted a USDA grant and that reviewers had raised concerns an ELISA method would not be capable of distinguishing between inactive LH beta subunits and active LH heterodimers. The lack of discrimination would limit the ability of an ELISA method to accurately measure product activity. Consequently, the sponsor now plans to explore development of an *in vitro* bioassay as an alternative or supplement to an ELISA method.

CVM stated that there was insufficient opportunity to read and comment on the sponsor's new document in detail, and without information on the manufacturing process, the appropriateness of an assay or purity method cannot be evaluated. For example, without knowledge of what in-process controls are used, the adequacy of end-product testing cannot be assessed.

CVM stated that if an *in vitro* bioassay is used to monitor product activity, a correlation should be demonstrated between *in vitro* bioassay test results and *in vivo* product effectiveness. Specifications (acceptable limits) for the *in vitro* test results would need to be proposed, and these specifications should be based on effectiveness results. CVM noted that an *in vitro* bioassay would by itself not measure product purity.

CVM agreed that an ELISA method would likely be inadequate by itself to accurately measure product activity and purity in their proposed crude tissue product. CVM explained that one of the tenets of the CMC technical section is to ensure consistent product quality across lots. One concern for a crude tissue product is that the profile of impurities in the product may change from lot to lot, potentially affecting product safety and effectiveness, or interfering with tests used to monitor product quality. The presence of gross impurities in a crude tissue product raises questions about impurities interfering with an ELISA method, what components in the tissue an ELISA method would actually be measuring, and the specificity of the antibodies used in the method.

CVM reminded the sponsor that the selected manufacturing process could dictate the types of methods chosen for quality control. For example, improving product purity via size exclusion may allow one to utilize methods like an ELISA that would not ordinarily be suitable to monitor the quality of a crude tissue product.

The sponsor stated that any purification of the pituitary gland tissue would be too costly, making the product financially unfeasible. CVM suggested that cost of testing also be factored into the total cost of production, not just cost of purification. A less purified product may need more complex test procedures, whereas testing a more purified product may be less expensive. CVM suggested that the sponsor also consider that testing will need to be performed post-approval for routine release and stability testing for as long as the product is marketed.

CVM stated that, regardless of the test methods used, the test article (clinical lots) used in the clinical studies should be manufactured and evaluated using the same formulation, processes (of appropriate scale) and test methods ultimately proposed in the CMC technical section and intended for marketed product. This aids in maintaining a quality bridge from the test article used in safety and effectiveness studies to the marketed product.

To help the sponsor understand how CVM approaches the evaluation of a test method in the context of a product, CVM provided examples of basic questions and issues that may be of concern when evaluating an assay method. Examples included the composition of the product, including the identity of active components, whether the pituitary gland contains a mixture of active hormones, and if the assay method accurately measures the components responsible for activity in effectiveness studies. CVM would also want to know the manufacturing process, including how potential contamination of adventitious agents (e.g., viruses) will be controlled. If the product label instructions for use are given relative to crude pituitary gland weight, will the activity per weight be verified by testing for each lot of product? If there are minimum or maximum limits in the concentration of active ingredient needed for the product to be effective, will the product be tested to verify the lot of material is within these limits? How will shelf-life of the product be tested?

CVM stated that the MOC will include reference to a guidance document pertaining to evaluation of viral clearance in animal tissue-derived products (see Appendix). The guidance can be downloaded from the FDA website.

CVM and the sponsor agreed that additional meetings and discussions focusing on CMC issues will be needed. CVM gave Mr. Daniel Burnette (telephone: 240-276-8264) as the contact person if the sponsor wishes to arrange a CMC meeting.

The sponsor also submitted the following agenda items for discussion:

2. We request that CVM's Product Chemistry Team provide information on assays or techniques that were considered to demonstrate product purity and manufacturing consistency.

CVM explained that assay techniques and manufacturing procedures used by other manufacturers are proprietary, and CVM cannot discuss this information.

3. Can the sponsor compete for OMUMS Grant funds to develop the assay described above (or an alternate assay suggested by CVM)?

CVM recommended that the sponsor contact OMUMS to obtain information on grant eligibility.

Effectiveness and Target Animal Safety Comments

The sponsor submitted their proposed approach to aspects of the Effectiveness and Target Animal Safety technical sections prior to the meeting. CVM responded to specific points of the proposal as described below. Additionally, CVM asked for clarification on the intended dose and dose administration regime. The sponsor indicated that they plan to pursue a total dose of 10 mg/kg body weight, administered as intraperitoneal injections of 2 mg/kg and 8 mg/kg separated by an 18 hour interval. The sponsor stated that they are planning to pursue an initial indication for use as a spawning aid in female channel catfish. CVM

recommended that all study protocols be submitted for review and concurrence prior to conducting any studies.

CVM also stressed the importance of conducting the safety and effectiveness trials with the final formulation of the product. CVM recommended that the sponsor resolve any CMC concerns that might require changes to the manufacturing process prior to conducting pivotal safety or effectiveness trials since such changes could affect the safety or effectiveness profile of the drug.

Effectiveness

Trial location: The sponsor hopes to be able to conduct two trials, at separate locations. However, if they are unable to use the second location, they would like to be able to conduct both trials at a single site. CVM stated that two sites are preferable. If the sponsor must use a single site, the two trials should be independent – conducted at different times, by different investigators, and using different genetic stocks of fish.

Fish stocks and timing: CVM stated that regardless of trial location, the stocks of fish used in the trials should be representative of stocks used in the industry, and distinct from each other. CVM stated that it would not be necessary for the trials to be conducted at any specific time during the spawning season unless the trials are conducted at the same site. If the trials are conducted at the same site they should be conducted at separate times in order to reinforce the independent nature of trials.

Effectiveness threshold and animal numbers: The sponsor proposed individual fish as the experimental unit and that effectiveness be demonstrated by two criteria: (1) statistical difference in ovulation rate between treated and control fish, and (2) the ovulation rate among the treated fish is > 60%. CVM stated that, aside from statistical significance from controls, there is no standard minimum success rate for reproduction drugs. However, the sponsor should consider what the industry would consider to be acceptable. If the sponsor thinks that an ovulation rate of at least 60% is needed for the drug to be considered successful in the field, the lower limit of a 95% confidence interval (CI) for the estimated success rate should be above 60%. This will likely mean using more animals than the 10 fish/group proposed by the sponsor. The estimated CI depends on the actually observed rate and the variance of that rate and, for binomial data, the variance is a function of observed rate. When success rate is close to 60%, the observed rate has a large variance; therefore, a narrower range and a larger sample size are required to meet the proposed criteria.

The sponsor stated that untreated control fish are expected to have very low ovulation rates – mostly 0%, but up to 5% in some cases. CVM indicated that because controls are expected to have a consistent ovulation rate near 0%, the trial could include fewer control fish than treated fish, for example the ratio of treated to control animals could be 2:1.

CVM noted that if fish are enrolled from different source ponds, that may need to be considered in the study design. For example, the source pond could be considered a blocking factor and randomization to treatment would be independent for each pond.

Inclusion criteria and enrollment: The sponsor proposed to include gravid (i.e. "almost ready to spawn") females in the effectiveness trials. CVM stated that this was acceptable, but that the criteria used to determine whether a fish is gravid or not should be described as clearly and objectively as possible in the protocol, in a manner that would allow an untrained person to understand why one fish is selected over another. Objective descriptions would also provide some assurance of consistency between trained personnel.

CVM stated that fish may be enrolled and randomly assigned to a treatment group in the study as they become ready. A "convenience" block may be used so that fish are enrolled in the treated and control groups in nearly the target ratio each day (ex. 1 control and 2 treated fish for each group of three fish). CVM also stated that it will be important for the sponsor to justify the number of fish screened and selected on each day, so that the process is similar to field conditions and ideal fish are not 'cherry picked' for use in the study.

Post injection assessments: The sponsor proposed to assess egg production 26-36 hours after the final injection. CVM asked what would happen to fish that ovulated before or after this timeframe. The sponsor stated that fish which ovulated prior to 26 hours or after 36 hours would be considered failures. CVM stated that this was acceptable, but that a wider window for ovulation may also be acceptable and that the sponsor may be placing unnecessary restrictions on the effectiveness trial by focusing on a timeframe that is linked to a specific production setting. The sponsor stated that fish would be kept in individual bags and monitored for egg release which will indicate that a fish is ready to strip spawn. CVM stated that the holding conditions sound acceptable and recommended that the sponsor provide more detail about the monitoring schedule and egg release criteria in the protocol. The sponsor proposed that eggs produced in response to stripping would be measured volumetrically and the release of > 100mL of eggs would constitute an ovulation success. Egg quality would be characterized as adequate or not adequate based on visual criteria (ex. white vs. yellow, clumpy vs. not clumpy). CVM agreed with the use of volumetric measurement, and a minimum volume of 100 mL. CVM recommended that more objective criteria be included in the protocol to define the visual criteria for egg quality. These could include the use of an ordinal scale (for example 0, 1, 2... where each number corresponds to some defined, meaningful difference in clumpiness). CVM stated that it will be important to define how these criteria relate to treatment success or failure.

Potential pursuit of a broader claim: CVM and the sponsor discussed the potential of pursing a broader "catfish" or "freshwater reared warmwater fish" indication. CVM stated that more information about the expected use pattern would be needed before species could be recommended for additional effectiveness trials to support a broader claim. If there is another warmwater species that would represent a major market, effectiveness information would likely be needed for that species. A warmwater fish indication could potentially include use in the ornamental fish industry, so effectiveness data from representative ornamental species may be important. Additionally, luteinizing hormone (LH) is understood to be the component of fish pituitary extracts which is responsible for inducing final oocyte maturation. LH is not as highly conserved as hormones further up the reproductive cascade and can have very species specific activity due to differences in peptide sequence and receptor binding. There are two distinct LH/LH receptor types found in fish species. It is likely that CVM would recommend that effectiveness be demonstrated in a fish that contains the alternate form of LH/LH receptor in order to support an all warmwater finfish claim. The sponsor should discuss an expanded claim with CVM prior to selecting species for additional effectiveness studies. The sponsor mentioned that they have spoken with Craig Watson regarding the potential of pursuing use in ornamental catfishes of the order Siluriformes.

Target Animal Safety (TAS)

Fish selection: The sponsor proposed to conduct a TAS study in 2 year old female channel catfish, in spawning season. CVM agreed with this approach and recommended that the study use clear enrollment criteria for gravid females, as discussed for the effectiveness studies.

Study conduct: The sponsor requested that the study be conducted in accordance with Guidance Document #85 and not be required to follow Good Laboratory Practice (GLP) standards. CVM indicated that the study should follow GLP standards as closely as possible and that the sponsor should discuss potential GLP deviations, along with their effect on the outcome of the study, with CVM during protocol development. CVM would make a determination regarding the deviations during its review of the protocol.

Doses for TAS study: The sponsor proposed to test 0X, 1X, 2X, and 3X the proposed dose. CVM agreed with this approach. Higher doses such as 10X, which was initially proposed, are not preferred for the evaluation of hormonal products since such doses may result in a negative feedback response which would not provide useful safety information.

Evaluation: The sponsor proposed to use 10 fish per treatment group; not to strip spawn the fish; to observe mortality, behavior and pathologies for 48 hours following treatment; and to evaluate the standard battery of tissues. CVM indicated that this approach is acceptable.

Expansion of the claim: For an all warmwater fish claim, the sponsor proposed to conduct a second TAS study on a separate fish species. The sponsor also indicated that they might be interested in a claim that includes only blue and channel catfish. CVM stated that a single TAS study may be sufficient for a broader claim but that the species used in the study should be justified based on the relative susceptibility of the fish included in the expected pattern of use.

All Other Information (AOI) Comments

CVM encouraged the sponsor to submit any relevant AOI with each Technical Section Complete (TSC) request. For example, submit the Effectiveness AOI with the last pivotal efficacy study/request for TSC. All relevant AOI that has not been included in the phased submissions throughout the INAD submissions will be submitted as an M submission when the last technical section is under review. The M should be submitted no later than 80 days after submission of the last technical section.

Labeling Comments
CVM encouraged the sponsor to submit the relevant portion of the label in each TSC request through the phased submissions. When the last technical section is under review, the sponsor will need to submit the complete label as an M submission for review. The M should be submitted no later than 80 days after submission of the last technical section.

Presubmission Conference Agreements

CVM and U.S. Fish and Wildlife reached the following agreements during this meeting:

1. The sponsor will conduct two independent studies - both at different times and by different investigators and with distinct stocks of fish that are representative of commercial fish stock.
2. CVM agreed with the sponsor's recommendation to provide examples of States that have regulatory programs or systems for permitting and/or containment of non-indigenous species in the EA.

Action Items

1. The sponsor will contact Dan Burnette in the Division of Manufacturing Technologies to set up a specific meeting to discuss CMC.

2. The sponsor will send a detailed description of manufacturing process to Division of Manufacturing Technologies. CVM will provide guidance through formal and informal teleconferences.

Appendix

Guidance for Industry Q5A - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin